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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,442	BRAUN ET AL.	
	Examiner	Art Unit	
	Maria Leavitt	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-01-2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant response of 01-16-2007 has been entered. With regard to restriction requirements, Applicant election **with traverse** of the following species is acknowledged: c-myc as a specifically named mRNA as recited in Claim 7, Gadolinium (Gd) as recited in claim 9 and polylysine as recited in claim 12.

Response to arguments

Applicant traversal is that the species of Group I, the specifically named mRNAs, are related by a "commonality of operation, function and effect" as they are all capable of hybridizing with the antisense peptide nucleic acid (PNA) as described in claim 4. Such is not persuasive.

The expression "special technical features" is defined in PCT Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. The determination is made on the contents of the claims as interpreted in light of the description and drawings (if any). In the instant application, Claim 4, encompass a genus of PNA able to hybridize any number of unidentified genes including myc-, c-ras-, hern-,etc. Each one of these genes comprises a distinct sequence with a pattern of nucleotides residues, wherein a specific and special mutation is made in order to confer a desired function. . For example, the as-filed specification discloses on page 16, paragraph 1, that ACGT comprising the PNA is targeted to a region of Exon II of the c-myc mRNA to prevent translation of the exon. In order words, the PNAs of the instant invention target very specific sequences for the intended purpose of diagnosing tumor cell. Hence, all the claimed PNA sequences in the as-filed

specification do not constitute a special technical feature, because under PCT Rule 13.2 for the reasons above.

Moreover, on page 3 of applicants remarks, Applicants argue that "spacer I and spacer II do not both comprise polylysine and/or polyglycine, but spacer I comprises polycysteine and spacer II comprises polylysine and the diagnostic conjugate, as set forth in the specification at pages 6-7 is coupled to spacer I and/or spacer If. Therefore choosing between polylysine and polyglycine is unnecessary, as these are separate parts of the same invention". Such is not persuasive.

Claim 12, as written, can be broadly interpreted as either or both, spacer I and spacer II, comprising a polylysine or polyglycine. Amending claim 12 to state that "spacer I comprises polycysteine and spacer II comprises polylysine" would clarify the meaning of the claim.

The requirement is still deemed proper and made Final.

Therefore, claims 1-16 are pending to which the following grounds of rejection are applicable.

Nucleotides and/or amino acid sequencesNotice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

This application contains sequence disclosure that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821. (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the

reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Specifically the application fails to comply with CFR 1.821 (d), which states: (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application. The specification discloses specific amino acid sequences on page 4, paragraph 4, and in claim 3; and an oligonucleotide sequence on page 6, paragraph 1, and in claim 8, all of which lack sequence identifiers. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and that otherwise meets the criteria of 37 CFR 1.821(a), must be set forth in the "Sequence Listing". (see MPEP 2422.03). Applicant is required to comply with the Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures by amending the specification and claims to include the appropriate SEQ ID NOS following each recitation of an amino acid sequence or nucleotide sequence meeting the criteria of 37 CFR 1.821(a).

Claim 9 is objected to because of the following informalities: Claim 9 is objected because of the use of the following abbreviations: Gd, Fe or F. Abbreviations should be spelled out at their first encounter in the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112-second paragraph-

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 provides for the use of a diagnostic, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 16 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

It is noted that if claim 16 is amended to a method claim, the method claim may be subject to further restriction since the instant claims under examination are drawn to products not methods

35 USC § 112- First paragraph- Written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to any person skilled in the art to which it pertains, or with which it is most nearly connected, at the time the application was filed, that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 1-16, encompass a genus of unspecified i) transmemembrane modules, ii) address modules, and iii) signaling modules. The as-filed specification defines the term "transmembrane module" of claim 1 as " a peptide or polypeptide that can penetrate the plasma membrane" (p. 4, paragraph 3). Moreover, claim 1 recites the term " an address module". The as-filed specification defines " an address module" as "a nucleic acid, a protein or peptide, a chemical substance etc" (p. 5, paragraph 2). Further, claim 1 recites the term " a signaling module " defined as as "is Gd, Fe or F" (page 6, paragraph 2). The term "transmembrane module" when given the broadest reasonable interpretation encompass any type of peptide or protein that can penetrate the membrane such a transmembrane proteins, signal peptides, ligand proteins of surface receptors. The term "address module" when given the broadest reasonable interpretation encompass any molecule e.g., antibodies, antisense RNA, PNAs. The term "a signaling module" encompass any type of radiological contrast agent, e.g., iron, copper, neodymium, cobalt, nickel.

In relation to a "transmembrane module" (TPU), Applicant discloses in the specification that preferred TPUs are derived from the penetratin family or transportan, and discloses three peptides of SEQ ID Nos. 2, 3 and 4 as TPU that are coupled to the address module (AS) via a

covalently cleave spacer I (p. 6, last paragraph) resulting in the products Nos. 3723, 3724 and 3725 (Table 1, column of product No.)

In so far as " an address module" the specification teaches on page 6, the peptide nucleic acid (PNA) of nucleotide SEQ ID No. 5. The coupling of the PNA complementary to the mRNA Myc Exon II generates the product No. 12a (Table 1). Additionally, the specification teaches the generation of a random antisense as product No. 12b. Protected peptide-DTPA (e.g., Diethylenetriamine-pentaacetic Acid) synthesis generating both the Cys-antisense –DTPA and Cys random-sequence-DTPA is disclosed on pages 9 and 10.

In so far as the "signaling module", the specification teaches that "said atoms or ions are linked to the address module as a chelate complex" using DTPA and the chelating agent. (p. 6, paragraph 2). Specifically, product # 153a (i.e., ACGT), and product # 153b (i.e., RCGT) are generated by solving stochiometric amounts of peptide-DTPA and the ion $Gd3^{+}$ (Sigma) resulting in the complexes $Gd3^{+}$-DTPH-lys-lys (linker)-Anti-Sense (PNA)-Cys –TPU constructs (p. 11, paragraph 1; table 1).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol.

66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan could determine the desired effect. Hence, the analysis below demonstrates that Applicant has not determined the core structure for full scope of the claimed genera.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure.

In relation to a "transmembrane module" (TPU), Applicant discloses three peptides of SEQ ID Nos. 2, 3 and 4 as TPU, however, the specification does not teach regions or domains of the peptide essential for the transmembrane module activity other than the three disclosed peptides. There is no teaching of how many amino acids may be deleted from either or both the N- and C-terminals and retain function or any structural features commonly possessed by members of the genus that distinguish them from other carrier or transmembrane module selected as a coupling partner of an AS other than the full length of SEQ ID Nos. 2, 3 and 4. Similarly, in relation to the address module, the specification teaches the nucleotide of SEQ ID No. 5 complementary to a region of a Exon II of the c-myc mRNA. However, the specification does not teach regions or domains of the address module is essential for activity other than the PNA of SEQ ID No. 5. There is no structure/function relationship taught at all for claimed

address modules other than the full length of nucleotide of SEQ ID No. 5. In the same way, only one example is disclosed for the signaling module, the $Gd3^{+}$-DTPH. There is no disclosure of any other contrast agents conjugated to the peptide-DTPA, nor disclosure of structure/function relationship taught at all for claimed signaling modules other than $Gd3^{+}$-DTPH. This disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims, as one of skill in the art cannot envision all variants having of contrast agents that can be used in nuclear medicine, MRT, PET, SPRCT, MR imaging or camera (p. 6, paragraph 1) .

Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g., amino acid sequence, nucleotide sequence, contrast agents), specific features and functional attributes (e.g., side chain protecting groups of PNA, binding of the TPU and AS by a redox coupling) that would distinguish different members of the claimed genus. In the instant case, no other characteristic in addition to the functional discussed above are disclosed. Such functional characteristics, however, do not allow one of skill in the art to distinguish the different members of the genera form each other.

Thus it is concluded that the written description requirement is not satisfied for the claimed genus of unspecified i) transmemembrane modules, ii) address modules, and iii) signaling modules.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A diagnostic conjugate for the molecular imaging of a human tumor expressing a c-myc gene comprising in sequential order:

a transmembrane transport peptide of SEQ ID Nos. 2, 3 or 4, conjugated via a cleavable linker to the antisense peptide nucleic acid of SEQ ID No. 5, conjugated via a linker to a $Gd3^{+}$ complex, wherein said target specific antisense conjugated $Gd3^{+}$ transporter complex is transported across the cell membrane, wherein a hybrid is formed of said an antisense peptide nucleic acid and the RNA target sequence, wherein said hybrid begins to be slowly enzymatically cleaved, thereby releasing the target specific antisense conjugated $Gd3^{+}$ transporter.

The specification does not provide an enabling disclosure for a diagnostic conjugate as broadly claimed. The specification teaches uptake by HeLa cervix carcinoma cells (e.g., comprise high levels c-myc mRNA) and Lymphocytes (e.g., undetectable c-myc mRNA) of conjugates $Gd3^{+}$-DTPH-lys-lys -Anti-Sense Cys –TPU constructs products #153a (i.e., ACGT, antisense), and #153b (i.e., RCGT, random) and evaluation of ACGT efflux in relation to RCGT by MR signal.

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Factors to be considered in determining whether a disclosure meets the enablement requirement

of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims, when given the broadest possible interpretation, encompass a diagnostic conjugate comprising a "transmembrane module" that can be broadly interpreted as any type of peptide or protein that can penetrate the membrane such a transmembrane proteins, signal peptides, ligand proteins of surface receptors, an "address module" encompassing any molecule e.g., antibodies, antisense RNA, PNAs and "a signaling module" broadly interpreted as any type of radiological contrast agent, e.g., iron, copper, neodymium, cobalt, nickel.

The specification provides insufficient data to enable claims directed to the method as broadly claimed. Thereby, specific issues including the functional limitations of a TPU, AS and SM that can read on a genus of polynucleotides, polypeptides and agents that have the functions of a diagnostic conjugate for the molecular imaging of tumors have to be examined and considered for patentability regarding the broadly claimed diagnostic conjugate.

In relation to a "transmembrane module" (TPU), the instant specification discloses on three peptides of SEQ ID Nos. 2, 3 and 4 as TPU, however, the specification does not teach regions or domains of the peptide essential for the transmembrane module activity other than the three disclosed peptides. Similarly, in relation to the address module, the specification teaches the nucleotide of SEQ ID No. 5 complementary to a region of a Exon II of the c-myc mRNA. In

the same way, only one example is disclosed for the signaling module, the $Gd3^{+}$-DTPH.

The skilled artisan understands that one nucleotide change in a DNA molecule or one amino acid change in the polypeptide encoded by the DNA molecule could result in the loss of its biological activity as demonstrated in the generation of sickle-cell anemia wherein on specific amino acid mutation gave rise to the inherited disease (Biochemistry John Wiley and Sons, 1990, p. 126-129). Since, the relationship between a sequence of a peptide and its tertiary structure is not well understood and is not predictable, it would required undue experimentation for one skilled in the art to arrive at other peptides that can function as a transmembrane transport unit to target specific antisense conjugated $Gd3^{+}$ transporter complex across the cell membrane. Moreover, in relation to antisense therapies, prior art teaches that sequence specific recognition between nucleic acids is critical for antisense annealing to its target in order to impair transcription, translation and/or destruction of the transcriptional /translational machinery (Schiavone et al., Current Pharmaceutical Design, 2004, pp. 769-784, p. 770, col. 2, paragraph 3). Since, the relationship between a sequence of a peptide and its tertiary structure is not well understood and is not predictable, it would required undue experimentation for one skilled in the art to arrive at other nucleotide / peptides sequences that can be use as a diagotic conjugate. In addition, in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 U.S.C. 112, first paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for the determination of other genetic

sequences that are embraced by the claim. This is the case here. In other words, since it would require undue experimentation to identify other TPU other than peptides of SEQ ID Nos. 2, 3 and 4 to be coupled to the AS via a covalently cleave spacer I, and other address modules other than the PNA of nucleotide SEQ ID No. 5 to generate an antisense-sequence-conjugated-Gadolinium-transporter, it certainty would require undue experimentation to make their corresponding DNA and, therefore, claims encompassing a genus of nucleic acids that may encode a TPU and an AS are not enabled by the claimed embodiment.

In relation to molecular imaging technologies, the art teaches a wide array of technologies based on contrast agents, radioactive isotopes, fluorescence labeling. For example, Berger et al., (2000, Breast Cancer Research) teaches the use of radioactive isotopes for imaging molecular events with SPECT and PET, however, this technique does not provide the high resolution anatomical imaging that is available by magnetic resonance imaging and computed tomography (p. 29, col. 1, paragraph 2). Similarly, Braun et al., (J. Mol. Bio. 2002, pp 237-243) visualize the targeting for a rhodamine- labeled 16-mer peptide nucleic acid covalently linked to a nuclear localization signal by confocal laser scanning microscopy. Thus in order to practice the claimed invention without any undue experimentation particularly in light of the unpredictability to make and use signaling module, one skilled in the Art would will have to perform extensive experimentation with each of signaling modules to find the embodiments embraced by Applicant' claims, and as such, this experimentation would be considered undue.

As set forth above by the nature of the invention, the state of the prior art, neither the prior art of record nor the as-filed specification provides sufficient guidance to enable a person skilled in the art to make and use a diagnostic conjugate for selective detection of cancer cells as

broadly claimed. As the result, given the unpredictability of the art and the lack of working example in the instant specification, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to practice the instant method to identify an enormous number of composition as broadly or generically claimed, with a resultant identification of a diagnostic conjugate for selective detection of cancer cells in a mammal as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of 35 U.S.C. 102(e) which forms the basis for all obviousness rejections set forth in this Office action:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4, 5, 6, 10, 12 15 and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by Collins et al, US Patent Application Publication 2006/0074034, Date of Publication April 6, 2007)

Collins et al , teaches a composition to deliver nucleic acids, analogs and derivatives (including antisense or stabilized antisense sequences) to desired locations to affect cell processes, including but not limited to gene transcription or translation (p. 9, [0059]; p. 9, [0096] [0097]) Specifically, Collins et al , discloses a compound comprising a carrier as vitamin B12, a ligand of a transcobalamin receptor or intrinsic factor receptor conjugated to nucleic acid,

peptide nucleic acid (PNA), in addition to a nuclear localization sequence (p. 9, [0105]; p. 10, [0121]). Moreover, Collins et al., teaches that "carriers of the present invention, can be labeled, for example with a detectable agent, such as a fluorescent marker, to provide detection of the hybridized complex" and discloses labels such as biotin, flourescent dyes, thiazole orange, fluorescin (p.35, [0332] [0333]). Collins et al , also discloses that "a detectable radionuclide (e.g. metallic radionuclide) or paramagnetic metal atom is linked to the residue of a compound of formula I by a suitable linker" (p. 47, [0406]). Specifically, "the linker can be a chelating group capable of chelating one or more detectable radionuclides (e.g. metallic radionuclides). More specifically, the linker can be a detectable chelating group. Specifically, the chelating group can be DTPA". (p. 47,[0414]). It is noted that DTPA is used in the instant invention to synthesize the peptide module. Current claims 1, 2, 4, 5 and 15.

Collins et al , teaches that parenchymal injection can be used to deliver the therapeutic composition directly to a tumorous growth (p. 48, [0421]). Current claims 6 and 16.

Collins et al, discloses that "the residue of an antisense sequence of the present invention can also be linked to the residue of a compound of formula I by a suitable linker" (p. 45,[390]). Current claim 10.

Collins et al , teaches that Linkers can comprise poly-L-lysine or multiple cysteines (p. 14, [0185]). Current claim 12.

Thus, Collins et al., teach all the claimed limitations and anticipates Applicant's claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1-7, 9, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Braun et al., (US patent No. 6,821,948), in view Cavaran et al.,. Bioconjug Chem. 1999 :361-70)

Braun discloses a conjugate comprising a penetratin constituent (e.g., transport mediator for the cell membrane), a nuclear localization signal (NLS) or address protein (Aps), a Polylysine Spacer and Rhodamine and an active substance (Abstract , Fig. 5, claim 7). Braun teaches that for "the introduction of active substances, in particular nucleic acids, "APs" are generally used which contain a cell-specific, compartment-specific or membrane-specific recognition signal, directing the attached active substance to its site of action" (col. 3, lines 12-16). Additionally, Brawn teaches examples of address proteins including SEQ ID No. 8, which presents a 100% homology to SEQ ID No. 3 disclosed in the instant invention (see SCORE Search Results for Application 10502442- SEQ ID Nos. 3 Resut 1). Moreover, Braun discloses a redox cleave site bewtween the transport mediator and the address protein/peptide. Braun teaches that the active substance can be a diagnostic agent and/or a therapeutic agent such as transcription factors, molecular probes, oligonucleotides, mRNA, mTRNA, antisense RNA, antisense oligonucleotides pharmaceutical active substances, chemotherapeutic agents, dyes, sensitizers, particles and said active substance may optionally be labeled, e.g. radioactively, with

a dye, with biotin/avidin, etc. (col. 4, lines 5-22). Moreover, Braun teaches that control conjugates were used in which rhodamine 110 was only bound to either penetratin or NLS (col. 7, lines 20-22). In Example 4, col. 8, lines 14-20, Braun exemplifies a peptide conjugate construct comprising a peptide nucleic acid (PNA), which is an antisense with respect to rats P2 promoter c-myc, resulting in inhibition of proliferation of AT-1 cells (rat prostate carcinoma) in relation to unligated control anti-sense sequences.

Brawn does not specifically teach the labeling of signaling modules with Gadolinium (Gd).

However, at the time the invention was made, Caravan et al., is an exemplified prior art that teaches that it is routine or well established in the art to employ gadolinium as a contrast agent with other antibodies or tissue specific molecules to provide disease specific MRI agents (p. 2340, col. 2, Table 23 and Table 24).

Thus, it would have been obvious for one of ordinary skill in the art of diagnostic conjugates to modify the label of the conjugated taught by Brawn to further employ a label of choice available in the art in the diagnostic conjugate. One of ordinary skill in the art would have been motivated to employ a Gadolinium as a label in order to enhance precision in diagnosis in cells by MRI imaging. One of ordinary skill in the art would have reasonably expected that conjugation of the contrast agent Gadolinium as a label that is routinely employed in the art could help to further depict disease specific MRI agents.

Conclusion

Claims 1-16 are not allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1636; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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